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(54) Title: FACTOR Xa INHIBITORS

(57) Abstract

The invention provides compounds which specifically inhibit factor Xa activity. The compounds consist of the structure X_1-YIR-X_2, wherein X_1 is H, acyl, alkyl, acylalkyl, arylalkyl or one or more amino acids, and X_2 is a modified C-terminal group, one or more carboxy-protecting groups or one or more amino acids or other substituent, and Y, I and R are tyrosine, isoleucine and arginine, respectively, or peptidomimetic or organic structures that possess the same functional activity as Y, I and R, respectively. In addition, the present invention provides a compound having the structure A1-A2-$(A3)_m$-B, where m is 0 or 1. A compound of the invention can be linear or cyclic and can be about 2 and 43 residues in length. A compound of the invention is characterized, in part, in that it exhibits a specific inhibition of factor Xa activity with a K_i of $\leq$ 100 μM, preferably $\leq$ 2 nM, and does not substantially inhibit the activity of other proteases involved in the coagulation cascade. The invention further provides methods of specifically inhibiting the activity of factor Xa and of inhibiting blood clotting *in vitro* and in an individual and methods of detecting factor Xa levels or activity.

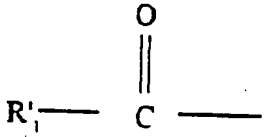
We claim:

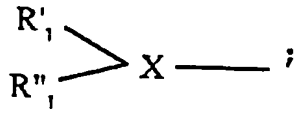
1. A compound that specifically inhibits the activity of factor Xa, having the general formula A1-A2-$(A3)_m$-B, wherein m is 0 or 1;

wherein A1 is R_1-R_2-R_3; A2 is R_4-R_5-R_6; A3 is R_7-R_8-R_9;

wherein R_1 is selected from the group consisting of:

i) 1 to 20 amino acids;

ii)  and

iii)  ;

wherein X is selected from the group consisting of N, CH and NC=O, and

wherein R'_1 and R''_1 independently are selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl and an amino-protecting group, and

wherein R_1 can be substituted by a substituent;

R_2 is $-CR_{99}R_{100}-$, wherein R_{99} and R_{100} independently are selected from the group consisting of an H; alkyl, arylalkyl, heteroarylalkyl and heteroaryl, and wherein R_{99} and R_{100} independently can be substituted with a substituent;

R_3 is selected from the group consisting of $-C(O)-$, $-CH_2-$, $-CHR_{99}-C(O)-$ and $-C(O)-NR_{35}-CH_2-C(O)-$, wherein R_{35} is the CHR_{55} group of the bridging group $-C(O)-CR_{55}-$;

R_4 is selected from the group consisting of $-CH_2-$ and $-NR_{50}-$, wherein R_{50} is selected from the group consisting of H, alkyl, arylalkyl and heterocyclic;

R_5 is $-CR_{201}R_{202}-$, wherein R_{201} and R_{202} independently are selected from the group consisting of H, alkyl, aryl and arylalkyl, and wherein R_{201} and R_{202} independently can be substituted with a substituent;

R_6 is selected from the group consisting of $-C(O)-$, $-CH_2-$ and $-CHR_{99}-C(O)-$;

R_7 is selected from the group consisting of $-CH_2-$ and $-NR_{51}-$, wherein R_{51} is H, alkyl, arylalkyl, heteroalkyl and heteroarylalkyl, and any of these moieties substituted by a substituent selected from the group consisting of Q and $-(CH_2)_n-Q$, wherein n is 1 to 5 and wherein Q is selected from the group consisting of an amino, amidino, imidazole and guanidino group, which can be substituted with a substituent, and a mono-, di-, tri- or tetra-alkylammonium of a pharmaceutically acceptable salt, isoureide or isothioureide thereof;

R_8 is $-CR_{210}R_{211}-$, wherein R_{210} and R_{211} independently are selected from the group consisting of H, alkyl, alkylaryl and heterocyclic, and any of these moieties substituted by a substituent selected from the group consisting of Q and $-(CH_2)_n-Q$, wherein n is 1 to 5 and wherein Q is selected from the group consisting of

amino, amidino, imidazole and guanidino group, which can be substituted with a substituent, and a mono-, di-, tri- or tetra-alkylammonium of a pharmaceutically acceptable salt, isoureide or isothioureide thereof;

R_9 is selected from the group consisting of $-C(O)-$, $-CH_2-$ and $-CHR_{99}-C(O)-$; and

wherein, when m is 1, B is selected from the group consisting of 1 to 20 amino acids, $-NHR_{52}$, $-NR_{60}R_{61}$, $-OR_{70}$ and $-CHR_{60}R_{61}$,

wherein R_{52} is selected from the group consisting of H, alkyl, arylalkyl, heteroarylalkyl and heteroaryl;

wherein R_{60} and R_{61} independently are selected from the group consisting of H, alkyl, arylalkyl, aryl, heteroarylalkyl and heteroaryl, and

wherein R_{70} is selected from the group consisting of H, acyl, alkyl, arylalkyl and heteroarylalkyl,

and wherein when m is 0, B is selected from the group consisting of 1 to 20 amino acids, $-OR_{70}$, $-NHR_{52}$ and $-NR_{60}R_{61}$, which is joined to R_6 by an amide bond or an ester bond;

wherein B can be substituted with a substituent,

provided that when R_3 is $-CH_2-$ or $-CHR_{99}-C(O)-$, R_4 is NR_{50};

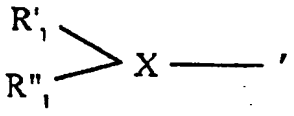
when R_4 is $-CH_2-$, R_3 is $-C(O)-$ or $-CHR_{99}-C(O)-$;

when R_4 is $-CH_2-$, R_3 is $-C(O)-$ or $-CHR_{99}-C(O)-$;

when R_6 is $-CH_2-$, R_7 is $-NHR_{51}-$;

when R_7 is CH_2, R_6 is $-C(O)-$ or $-CHR_{99}-C(O)-$;

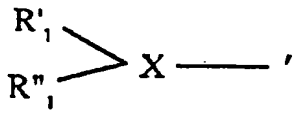
when R_4 is $-NR_{50}-$ and R_1 is



R_{50} and R'_1 are taken together to form a bridging group having the formula: $-C(O)-CHR_{55}-$,

wherein CHR_{55} represents R_{50} and the carbonyl group represents R'_1, and

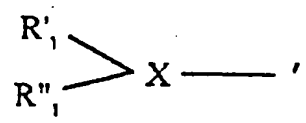
$R"_1$ and R_{55} independently are H, C_1 to C_6 alkyl or arylalkyl; and

when R_3 is $-C(O)-NR_{35}-CH_2-C(O)-$, then R_4 is $-NR_{50}-$, R_1 is  , R_{35} and R'_1 are taken together to form a bridging group having the formula $-C(O)CHR_{55}-$,

wherein C(O) represents R'_1 and CHR_{55} represents R_{35}; $R"_1$ and R_{55} independently are H or a C_1 to C_6 alkyl.

2. The compound of claim 1, wherein

R_4 is $-NR_{50}-$,

R_1 is  ,

R_{50} and R'_1 are taken together to form a bridging group of the formula $-C(O)-CHR_{55}$,

wherein R_{55} is H;

R_1 is H or methyl;

R_{99} and R_{100} independently are selected from the group consisting of H, arylalkyl, alkyl and heteroalkyl or 1 to 3 carbon atoms,

and wherein R_{99} and R_{100} can be further linked to a moiety selected from the group consisting of phenyl, thienyl, thiazolyl, pyridyl, naphthyl, thionaphthyl, indolyl or saturated alkyl, alkoxy, monoalkylamino, dialkylamino, tetraalkylammonium, arylalkylamino, aminoalkylaryl, carboxy, halo, hydroxy, amino, amido, amidino, guanidino, triazolyl and sulfonyl,

and R_3 is selected from the group consisting of $-C(O)-$ and $-C(O)-NR_{35}-CH_2-C(O)-$.

3. The compound of claim 1, further comprising a bridge formed between two moieties selected from the group consisting of R_{10} and R_1, R_9 and R_1, R_8 and R_1, R_5 and R_1, R_5 and R_2, R_5 and R_8, and R_5 and R_9,

wherein said bridge structure consists of the structure $-CR_{400}R_{410}$ $(X-Y)-R_{500}R_{510}C-$; wherein R_{400}, R_{410}, R_{500} and R_{510} are selected from the group consisting of H, alkyl, cycloalkyl, arylalkyl and aryl,

and X and Y independently are selected from the group consisting of carbon, nitrogen, oxygen, sulfur, -CO-NH-, $-CH_2-O-CH_2$, and functional equivalents thereof;

and wherein R_{400}, R_{410}, R_{500}, R_{510} can be substituted with a moiety selected from the group consisting of an alkyl group and a heteroatom.

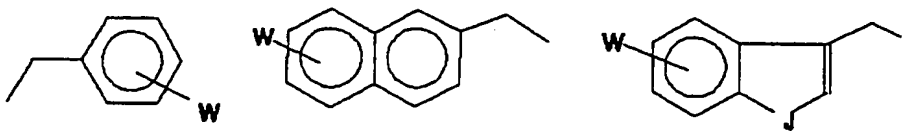
4. The compound of claim 1, wherein R'1 and R"1 independently are substituted by a substituent selected from the group consisting of a C_1-C_6 alkyl, $-OCH_2-$, $-SCH_2-$, $>N-CH_2-$, >N-C(O)-, -CO- and NY-CO-NZ,

wherein Y and Z independently are selected from the group consisting of H, C_1-C_8 alkyl, C_5-C_{12} arylalkyl and heteroarylalkyl.

5. The compound of claim 1, wherein R_2 is substituted by a substituent selected from the group consisting of phenyl, thienyl, thiazolyl, pyridyl, naphthyl, thionaphthyl, indolyl, alkyl, alkoxy, monoalkylamine, dialkylamine, tetraalkylammonium, arylalkylamino, aminoalkylaryl and carboxy.

6. The compound of claim 5, wherein R_2 is substituted with 1 to 5 substituents selected from the group consisting of alkyl, alkoxy, monoalkylamino, dialkylamino, tetraalkylammonium, arylalkylamino, aminoalkylaryl, carboxy, halogens, hydroxy, amino, amido, amidino, guanidino, triazolyl and sulfonyl.

7. The compound of claim 1, wherein R_{100} is H and R_{99} is selected from the group consisting of:



wherein W is selected from the group consisting of H, amino, lower alkyl, optionally substituted by an amine, amide, hydroxyl, carboxyl and amidino;

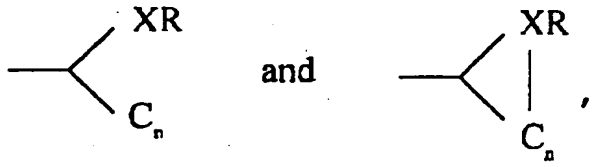
and J is selected from the group consisting of oxygen, sulfur, NH and NR, wherein R is selected from the group consisting of C_1-C_6 alkyl, C_5-C_{12} arylalkyl, C_1-C_6 alkanoyl and C_5-C_{12} aryloyl.

8. The compound of claim 1, wherein R_{50} is substituted by a substituent selected from the group consisting of an N-, O- and S-containing moiety.

9. The compound of claim 1, wherein R_{50} is selected from the group consisting of H, alkyl, arylalkyl and heteroarylalkyl.

10. The compound of claim 1, wherein R_{201} and R_{202} further is substituted by a substituent selected from the group consisting of an N-, O- and S-containing moiety.

11. The compound of claim 1, wherein R_{202} is H and R_{201} is selected from the group consisting of



wherein X is C, N or S, and wherein R is selected from the group consisting of H and an alkyl, which can be substituted by a heteroatom; and n is 1 to 5.

12. The compound of claim 1, wherein R_{51} is substituted by a substituent selected from the group consisting of a N-, O- and S-containing moiety.

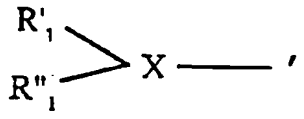
13. The compound in claim 1, wherein R_{210} or R_{211} is substituted with a substituent selected from the group consisting of Q and $(CH_2)_n$-Q, wherein n is 1 to 5.

14. The compound of claim 1, wherein R_{52} is substituted by a substituent selected from the group consisting of a N-, O- and S-containing moiety.

15. The compound of claim 1, wherein R_{60} and R_{61} independently are substituted by an alkyl.

16. The compound of claim 1, wherein R_{70} is substituted by an alkyl.

17. The compound of claim 1, wherein:

R_1 is  ,

R'_1 is selected from the group consisting of H, $-CO-R_a$, $-SO_2-R_a$, an amino-protecting group, 1 to 6 amino acids, which can be substituted, wherein the N-terminus of said 1 to 6 amino acids is substituted with a substituent selected from the group consisting of H, $-CO-R_a$, $-SO_2-R_a$ and an amino-protecting group; and

wherein R_a is selected from the group consisting of alkyl, aryl and heteroalkyl;

$R"_1$ is selected from the group consisting of H, acyl and alkyl;

X is N;

R_2 is $-CHR_{99}-$, wherein R_{99} is selected from the group consisting of alkyl, aryl, arylalkyl, heteroalkyl and heteroaryl, which can be substituted with a substituent selected from the group consisting of 1 to 6 fluoro, chloro, bromo, iodo, amino, nitro, amidino, amido, carboxy, ester, ether and hydroxy groups;

R_3 is $-C(O)-$;

R_4 is $-NH-$;

R_5 is $-CHR_{201}-$, wherein R_{201} is an alkyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

R_8 is $-CHR_{210}-$, wherein R_{210} is a heteroalkyl having at least one formal positive charge, wherein the heteroatom is N;

R_9 is $-C(O)-$; and

B is selected from the group consisting of $-OR_b$ and $-N-R_cR_d$,

wherein R_b is selected from the group consisting of H, alkyl and a carboxy-protecting group,

R_c is selected from the group consisting of H and alkyl, and

R_d is selected from the group consisting of alkyl, heteroalkyl and 1 to 20 amino acids, which can be substituted with a substituent,

wherein the C-terminus of said compound can be modified with a carboxy-protecting group, a primary amide group or part of a cyclic peptide as the secondary or tertiary amide group formed with amino group of R_1.

18. The compound of claim 17, wherein A1 is selected from the group consisting of Tyr, F(pNH_2), mAph, pAph and Nal(2).

19. The compound of claim 17, which contains an amino-protecting group.

20. The compound of claim 17, wherein A2 is selected from the group consisting of Ile and Chg.

21. The compound of claim 17, wherein A3 is selected from the group consisting of Arg, PalMe(3), Dab(N^{γ}-C_3H_7N), Dap(N^{β}-C_3H_7N) and Orn(N^{δ}-C_3H_7N).

22. The compound of claim 17, wherein

A1 is selected from the group consisting of Tyr, F(pNH_2), mAph, pAph and Nal(2), which contain 0 or 1 amino-protecting groups;

A2 is selected from the group consisting of Ile and Chg;

A3 is selected from the group consisting of Arg, PalMe(3), Dab(N^{γ}-C_3H_7N), Dap(N^{β}-C_3H_7N) and Orn(N^{δ}-C_3H_7N); and

B is selected from the group consisting of -H, -OH, -NH_2, one to five amino acids or functional equivalents thereof and a carboxy-protecting group.

23. The compound of claim 22, which is selected from the group consisting of:

Ac-pAph-Chg-PalMe(3)-NH-CH_2-Chx;
Ac-pAph-Chg-PalMe(3)-NH-2CMT;
Ac-pAph-Chg-PalMe(3)-NH-Chx;
Ac-F(pNH_2)-Chg-Dab(N^{γ}-C_3NH_7)-L-P-NH_2;
Bz-F(pNH_2)-Chg-R-L-P-NH_2;
Tos-F(pNH_2)-Chg-R-L-P-NH_2;
Ac-Y(3-I)-Chg-R-L-P-NH_2;
y-Chg-R-L-NH_2;
Ac-F(pNH_2)-Chg-R-ol;
Cyclopentyl-CO-pAph-Chg-PalMe(3)-NH_2;
3-Iqc-pAph-Chg-PalMe(3)-NH_2;
Bzf-pAph-Chg-PalMe(3)-NH_2;
3-Iqc-F(pNH_2)-Chg-R-L-P-NH_2;
Ac-F(pNH_2)-Chg-R-NH-2-thiazolyl;
2-Furoyl-pAph-Chg-PalMe(3)-NH_2;
5-Me-2-thienyl-CO-pAph-Chg-PalMe(3)-NH_2;
Ac-Nal(2)-Chg-R-NH-2-thiazolyl;
2-Bzf-F(pNH_2)-Chg-R-L-P-NH_2;
Ac-pAph-Chg-Dab(N^{γ}-C_3H_7N)-L-P-NH_2;
Ac-(iBu)pAph-Chg-R-L-P-NH_2;
Ac-pAph-Chg-R-Gla-P-NH_2;

Ac-pAph-Chg-R-Pen(CH_2COOH)-P-NH_2;
Ac-pAph-Chg-R-L-P-NH_2;
Ac-F(pNH_2)-Chg-R-(Me)L-P-NH_2;
Ac-F(pNH_2)-Chg-R-OEt;
Ac-F(pNH_2)-Chg-Orn(N^{δ}-C_3H_7N)-L-P-NH_2;
Ac-F(pNH_2)-Chg-R-L-P-NH_2;
Ac-Nal(2)-Chg-R-L-P-NH_2;
Ac-pAph-Chg-Dab(N^{γ}-C_3H_7N)-NH_2;
Ac-pAph-Chg-PalMe(3)-NH_2;
Ac-pAph-Chg-PalMe(3)-L-P-NH_2;
Ac-pAph-Chg-R-NH_2;
Ac-pAph-Chg-R-OH;
Ac-pAph-Chg-R-ol;
DIPA-(m)pAph-Chg-R-L-P-NH_2;
DIPA-(m)F(pNH_2)-Chg-R-L-P-NH_2;
Isn-F(pNH_2)-Chg-R-L-P-NH_2;
Pza-F(pNH_2)-Chg-R-L-P-NH_2;
Tfa-(iBu)Y-Chg-R-L-P-NH_2; and
Tfa-(iBu)Y-I-Orn(N^{δ}-C_3H_7N)-L-P-NH_2.

24. The compound of claim 22, selected from the group consisting of:
Ac-pAph-Chg-PalMe(3)-NH-CH_2-Chx;
Ac-pAph-Chg-PalMe(3)-NH-Chx;
Bzf-pAph-Chg-PalMe(3)-NH_2;
Ac-pAph-Chg-PalMe(3)-L-P-NH_2;
Ac-pAph-Chg-PalMe(3)-NH_2;
Cyclopentyl-CO-pAph-Chg-PalMe(3)-NH_2;
3-Iqc-pAph-Chg-PalMe(3)-NH_2;
2-Furoyl-pAph-Chg-PalMe(3)-NH_2;
5-Me-thienyl-CO-pAph-Chg-PalMe(3)-NH_2; and
Ac-pAph-Chg-PalMe(3)-ol.

25. The compound of claim 1, wherein m is 0.

26. The compound of claim 25, wherein B is a heteroarylalkyl.

27. The compound of claim 26, wherein said heteroarylalkyl is selected from the group consisting of:
(4-(N-methylpyridinium))methyl;
2-(3-(N-methylpyridinium))eth-1-yl;
1-(4-(N-methylpyridinium))eth-1-yl;
(p-amidino)benzyl;
2-(4-(N-methylpyridinium))prop-2-yl; and
2-(4-(N-methylpyridinium))eth-1-yl.

28. The compound of claim 26, which is selected from the group consisting of:
Ac-pAph-Chg-AMP(4) and
Ac-pAph-Chg-AEMP(4).

29. A non-naturally occurring compound which specifically inhibits factor Xa activity, having the structure X_1-YIR-X_2,

wherein X_1 is selected from the group consisting of H, acyl, alkyl, acylalkyl, arylalkyl and 1 to 20 amino acids, and

X_2 is selected from the group consisting of a modified C-terminal group, one or more carboxy-protecting groups and 1 to 20 amino acids,

wherein said compound can be substituted with a substituent.

30. The compound of claim 29, wherein X_1 is selected from the group consisting of H, 1 amino acid and 2 amino acids and X_2 is selected from the group consisting of a modified C-terminal group, one or more carboxy-protecting groups and 1 to 17 amino acids.

31. The compound of claim 29, wherein said compound is linear.

32. The compound of claim 29, wherein said compound is cyclic.

33. The compound of claim 32, wherein the cyclization is through a bridge outside the YIR motif.

34. The compound of claim 33, wherein the cyclization includes a bridge with the Ile residue present within the YIR motif.

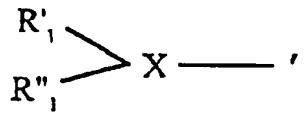
35. The compound of claim 29 selected from the group consisting of:

Ac-Tyr-Ile-Arg-Leu-Ala-NH_2,
Ac-Tyr-Ile-Arg-Leu-Pro-NH_2,
Ac-(iBu)Tyr-Ile-Arg-Leu-Pro-NH_2,
Ac-Tyr-Ile-Arg-$N(CH_3)O(CH_3)$,
Ac-Tyr-{$\Psi(CH_2NH)$}-Ile-Arg-Leu-Pro-NH_2,
Ac-Tyr-Ile-Arg-NH-CH_2(4-Pyridyl),
Ac-Tyr-Ile-{$\Psi(CH_2NH)$}-Arg-Leu-Pro-NH_2,
Ac-Tyr-Chg-Arg(NO_2)-{$\Psi(CH_2NH)$}-Leu-NH_2,
Ac-Tyr-Ile-Arg-{$\Psi(COCH_2)$}-Gly-Pro-NH_2,
Ac-Tyr-Ile-Dab(N^{γ}-C_3H_7N)-Leu-Ala-NH_2,
Ac-Tyr-Ile-PalMe(3)-NH_2,
Tyr-Ile-Arg-NH_2,
D-Tyr-Ile-Arg-Leu-Pro-NH_2,
Ac-(Bzl)Gly-(Chx)Gly-(3-guanidopropyl)Gly-NH_2,
Cyclo(Gly-Tyr-Ile-Arg-Gly),
Tfa-(iBu)Tyr-Chg-Arg-Leu-Pro-NH_2,
Ac-pAph-Chg-Arg-Leu-Pro-NH_2,
Ac-Nal(2)-Chg-Arg-Leu-Pro-NH_2,
Ac-pAph-Chg-PalMe-NH_2, and

pharmaceutically acceptable salts, amides, esters, alcohols and aldehydes thereof.

36. A method of specifically inhibiting the activity of factor Xa, comprising contacting the factor Xa with the compound of claim 1.

37. The method of claim 36, wherein

R_1 is  ,

R'_1 is selected from the group consisting of H, $-CO-R_a$, $-SO_2-R_a$, an amino-protecting group, 1 to 6 amino acids, which can be substituted, wherein the N-terminus of said 1 to 6 amino acids is substituted with a substituent selected from the group consisting of H, $-C(O)-R_a$, $-SO_2-R_a$ and an amino-protecting group; and

wherein R_a is selected from the group consisting of alkyl, aryl and heteroalkyl;

R''_1 is selected from the group consisting of H, acyl and alkyl;

X is N;

R_2 is $-CHR_{99}-$, wherein R_{99} is selected from the group consisting of alkyl, aryl, arylalkyl, heteroalkyl and heteroaryl, which can be substituted with a substituent selected from the group consisting of 1 to 6 fluoro, chloro, bromo, iodo, amino, nitro, amidino, amido, carboxy, ester, ether and hydroxy groups;

R_3 is $-C(O)-$;

R_4 is $-NH-$;

R_5 is $-CHR_{201}-$, wherein R_{201} is an alkyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

R_8 is $-CHR_{210}-$, wherein R_{210} is a heteroalkyl having at least one formal positive charge, wherein the heteroatom is 1 to 6 nitrogen atoms;

R_9 is $-C(O)-$; and

B is selected from the group consisting of $-OR_b$ and $-N-R_cR_d$,

wherein R_b is selected from the group consisting of H, alkyl and a carboxy-protecting group,

R_c is selected from the group consisting of H and alkyl, and

R_d is selected from the group consisting of alkyl, heteroalkyl and 1 to 20 amino acids, which can be substituted with a substituent,

wherein the C-terminus of said compound can be modified with a carboxy-protecting group, a primary amide group or part of a cyclic peptide as the secondary or tertiary amide group formed with amino group of R_1 or by reduction to the alcohol.

38. The method of claim 37, wherein

A1 is selected from the group consisting of Tyr, $F(pNH_2)$, mAph, pAph and Nal(2), which contain 0 or 1 amino-protecting groups;

A2 is selected from the group consisting of Ile and Chg;

A3 is selected from the group consisting of Arg, PalMe(3), $Dab(N^{\gamma}-C_3H_7N)$, $Dap(N^{\beta}-C_3H_7N)$ and $Orn(N^{\delta}-C_3H_7N)$; and

B is selected from the group consisting of -H, -OH, $-NH_2$, one to five amino acids or functional equivalents thereof and a C-terminus protecting group.

39. The method of claim 38, wherein said compound is selected from the group consisting of:

Ac-pAph-Chg-PalMe(3)-NH-CH_2-Chx;

Ac-pAph-Chg-PalMe(3)-NH-Chx;

Bzf-pAph-Chg-PalMe(3)-NH_2;

Ac-pAph-Chg-PalMe(3)-L-P-NH_2;

Ac-pAph-Chg-PalMe(3)-NH_2;

Cyclopentyl-CO-pAph-Chg-PalMe(3)-NH_2;

3-Iqc-pAph-Chg-PalMe(3)-NH_2;

2-Furoyl-pAph-Chg-PalMe(3)-NH_2;

5-Me-2-thienyl-CO-pAph-Chg-PalMe(3)-NH_2; and

Ac-pAph-Chg-PalMe(3)-ol.

40. The method of claim 38, wherein said compound is selected from the group consisting of:

Ac-Y-I-R-L-A-NH_2,

Ac-Y-I-R-L-P-NH_2,

Ac-(iBu)Y-I-R-L-P-NH_2,

Ac-Y-I-R-N(CH_3)O(CH_3),

Ac-Y-{Ψ(CH_2NH)}-I-R-L-P-NH_2,

Ac-Y-I-R-NH-CH_2(4-Pyridyl),

Ac-Y-I-{Ψ(CH_2NH)}-R-L-P-NH_2,

Ac-Y-Chg-R(NO_2){Ψ(CH_2NH)}-L-NH_2,

Ac-Y-I-R-{Ψ($COCH_2$)}-G-P-NH_2,

Ac-Y-I-Dab(N^{γ}-C_3H_7N)-L-A-NH_2,

Ac-Y-I-PalMe(3)-NH_2,

Y-I-R-NH_2,

D-Y-I-R-L-P-NH_2,

Ac-(Bzl)Gly-(Chx)Gly-(3-guanidopropyl)Gly-NH_2,

Cyclo(G-Y-I-R-G),

Tfa-(iBu)Y-Chg-R-L-P-NH_2,

Ac-pAph-Chg-R-L-P-NH_2,

Ac-Nal(2)-Chg-R-L-P-NH_2, and

pharmaceutically acceptable salts, amides, esters, alcohols and aldehydes thereof.

41. A method of inhibiting blood clotting in an individual, comprising administering the compound of claim 1 to the individual.

42. A method of diagnosing the level of factor Xa in a sample, comprising contacting the sample with the compound of claim 1 and detecting the amount of binding.

43. A method of diagnosing the level of active factor Xa in a sample, comprising contacting a sample with the compound of claim 1 and detecting the amount of factor Xa enzymatic activity.